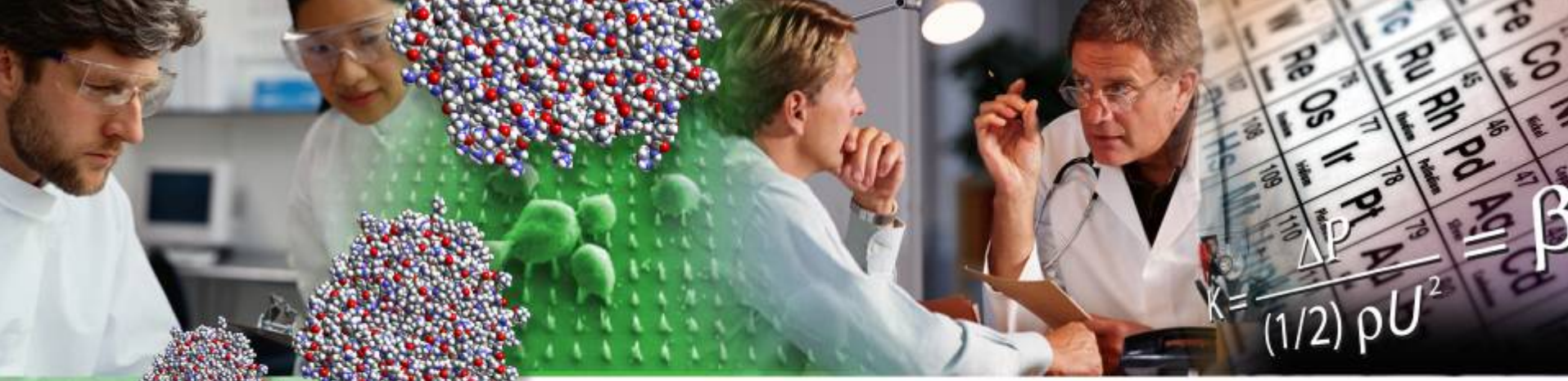


NNI at Five Years: Public Interest

Nanotechnology for Cancer Treatment

February 6, 2006

Gregory J. Downing, D.O., Ph.D.
Director, Center for Strategic Science and Technology Initiatives
National Cancer Institute

Potential of Nanotech Applications in Medicine

NCI Alliance for Nanotechnology in Cancer

Over the next several years, nanotechnology will enable a new generation of biomedical products that will:

- Drive major advances in diagnosis, treatment and prevention of cancer
- Improve the current drug discovery and development and regulatory review processes
- Introduce novel ways to bring therapeutics to market
- Catalyze new business models for industry

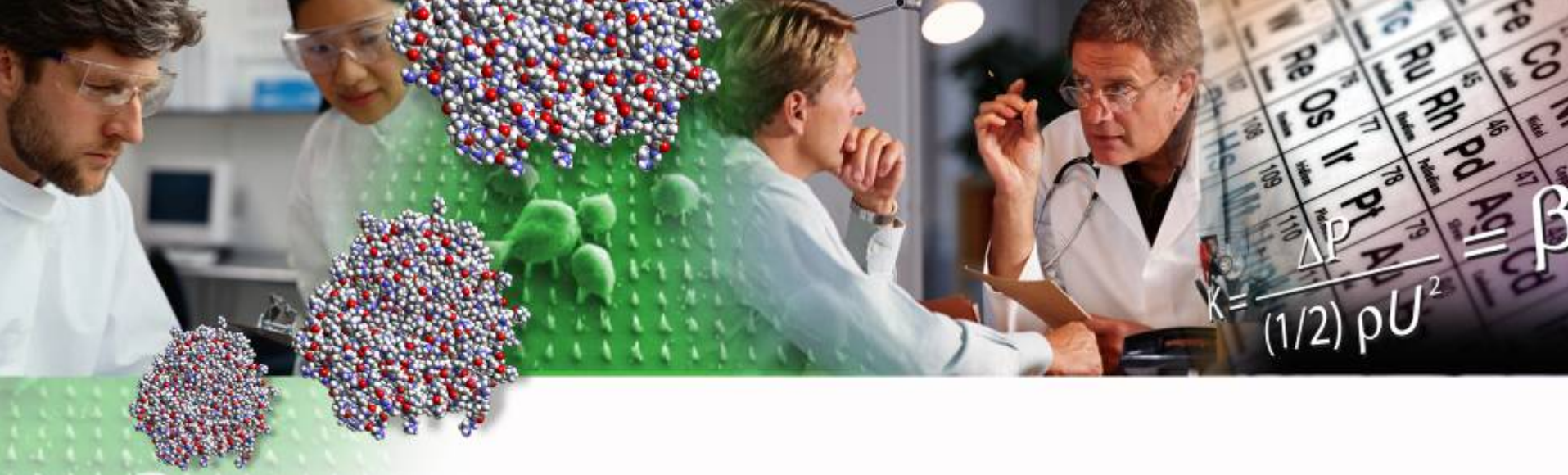
Why It's the Right Time: Science and Technology Development

NCI Alliance for Nanotechnology in Cancer

- The science is exploding
  - Major advances in genomics, proteomics, and materials science
  - Tidal wave of data on molecular underpinnings of disease and increased understanding of cancer mechanisms

- The nano-based biomedical technology candidates are expanding*
  - 68% increase in the clinical pipeline from 2005
  - 130 nanotech-based drugs and delivery systems
  - 125 devices or diagnostic tests

* Source: 2006 Nanomedicine, Device & Diagnostic Report, National Health Information, LLC.

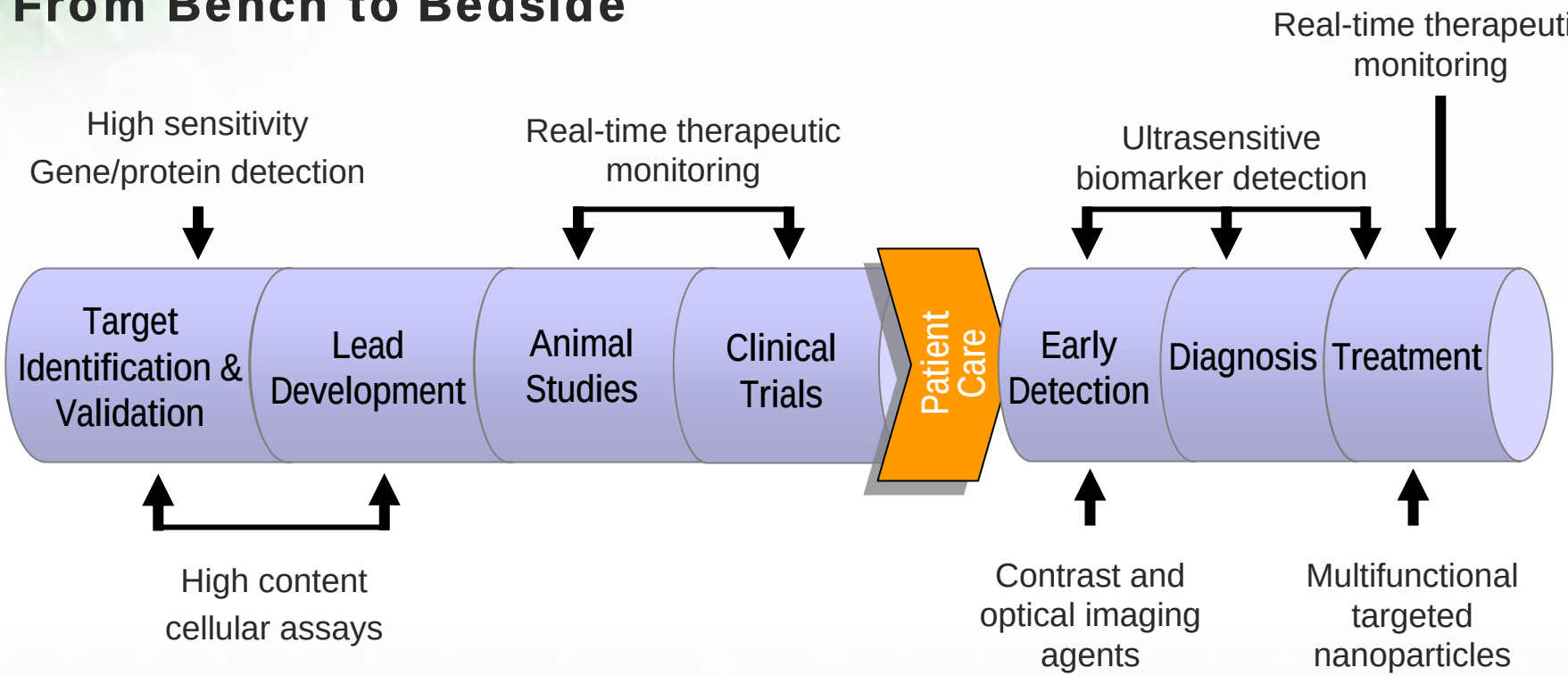


Scientific, Clinical and Commercial Potential of Nanotechnology in Cancer

Nanotech Has Multiple Applications

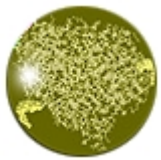
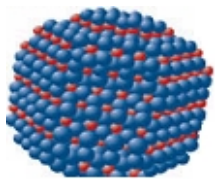
NCI Alliance for Nanotechnology in Cancer

From Bench to Bedside



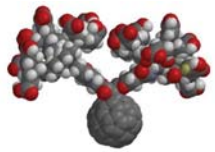
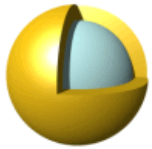
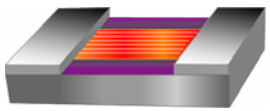
Nanotech "Toolbox"

NCI Alliance for Nanotechnology in Cancer

Modality	*Potential Applications*
Cantilevers 	• High-throughput screening • Disease protein biomarker detection • DNA mutation detection (SNPs) • Gene expression detection
Carbon Nanotubes 	• DNA mutation detection • Disease protein biomarker detection
Dendrimers 	• Target sequestration • Controlled release drug delivery • Image contrast agents
Nanocrystals 	• Improved formulation for poorly soluble drugs

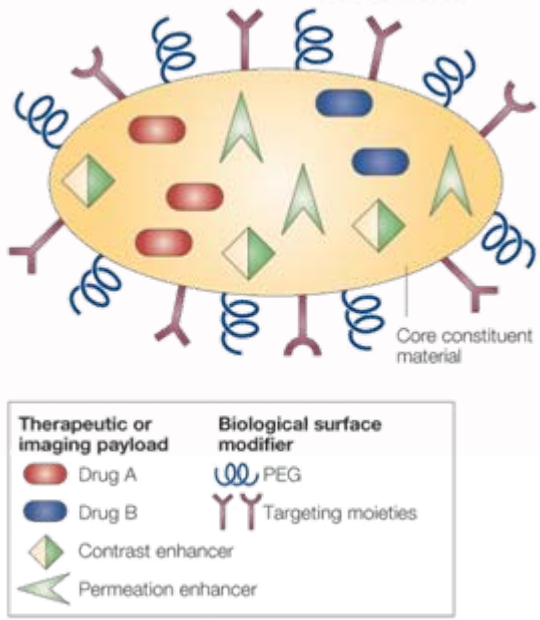
Nanotech "Toolbox"

NCI Alliance for Nanotechnology in Cancer

Modality	*Potential Applications*
Nanoparticles 	• Multifunctional therapeutics • Targeted drug delivery, permeation enhancers • MRI and ultrasound image contrast agents • Reporters of apoptosis, angiogenesis, etc.
Nanoshells 	• Deep tissue tumor cell thermal ablation • Tumor-specific imaging
Nanowires 	• High-throughput screening • Disease protein biomarker detection • DNA mutation detection (SNPs) • Gene expression detection
Quantum Dots 	• Optical detection of genes and proteins in animal models and cell assays • Tumor and lymph node visualization

Targeted Therapies

NCI Alliance for Nanotechnology in Cancer



Source: M. Ferrari, "Cancer Nanotechnology: Opportunities and Challenges," Nature Reviews, March 2005.

Problem:

- Current cytotoxic treatments have severe side effects
- Maintaining effective dose in circulation is difficult
- Multi-drug resistance

Solution:

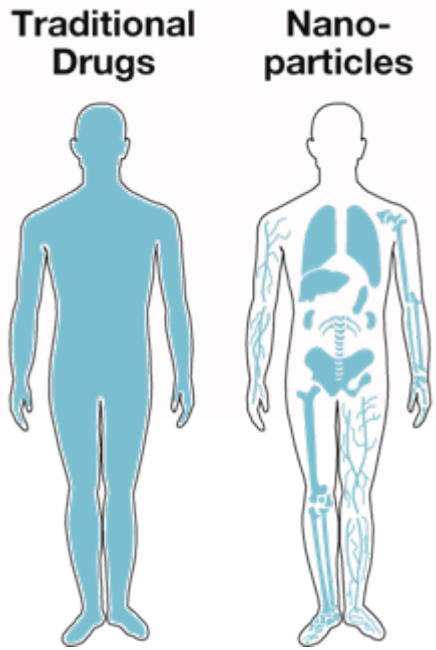
- Treatments for controlled and sustained delivery
- Drug-delivery systems that combine targeting agents with efficacy reporters
- Tumor-specific thermal ablation and/or photo sensitization
- Capability to overcome cellular transport mechanism responsible for drug resistance

Drug Delivery

NCI Alliance for Nanotechnology in Cancer

Problem:

- Non-specific
- Cannot reach tumor
- Insoluble
- Systemic chemotherapy is often toxic



Solution:

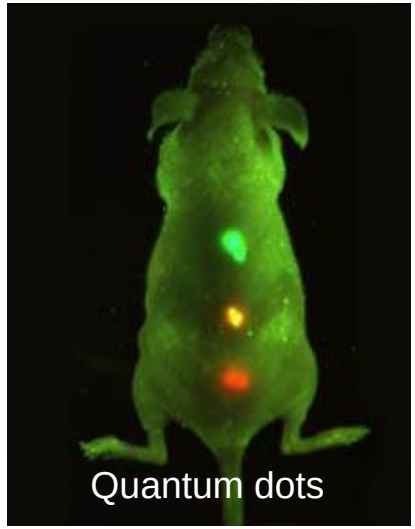
- Payload: large quantities of multiple drugs delivered directly to tumor sites
- Delivery device minimizes alterations needed to drug
- Therapeutic index shifts
- Enables nucleic acid delivery

In Vivo and Local Imaging

NCI Alliance for Nanotechnology in Cancer

Problem:

- Cancer metastasizes before it can be detected
- No reliable risk/exposure assays for carcinogenesis



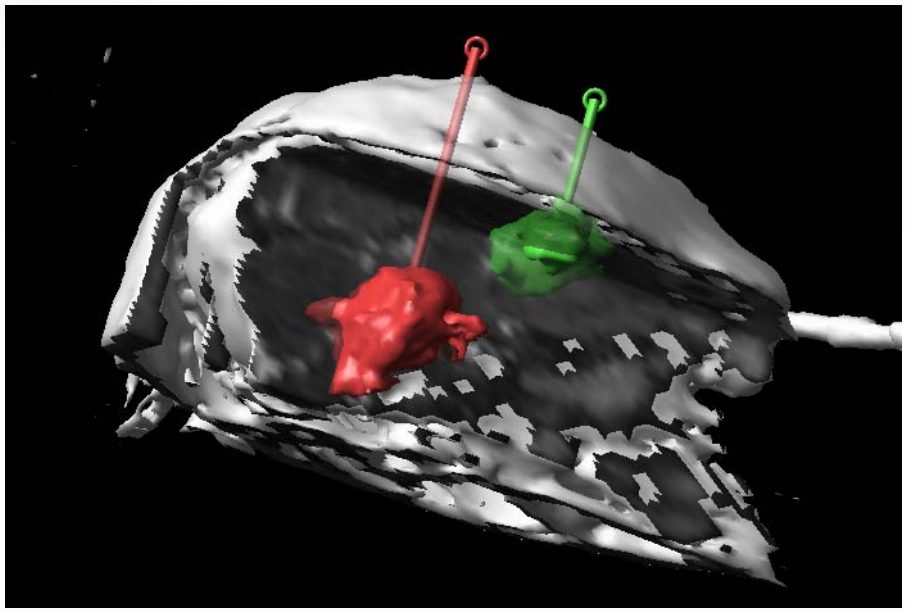
Source: Sh. Nie, JAMA, Vol. 292, No.16, p.1944-1945, 2004.

Solution:

- Multifunctional nanoparticles functionalized with specific antibodies decorate tumor cells
- Subsequent imaging allows for pinpointing of tumor cell conglomerates

Real-Time Monitoring of Drug Distribution in the Brain

NCI Alliance for Nanotechnology in Cancer



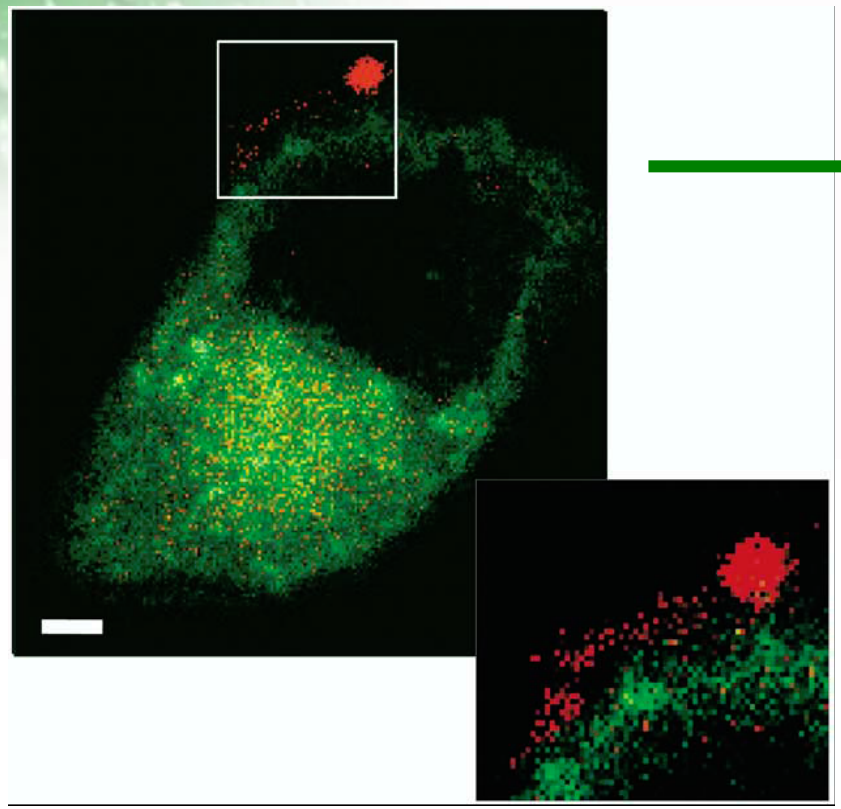
R. Saito, et al., *Experimental Neurology*, **196:**381-389, 2005

Study Results: This real-time MR image shows gadolinium-loaded nanoparticles that have diffused through two different regions of the brain when administered using convection-enhanced delivery.

Potential Clinical Advantage: Gd-loaded nanoparticles, used with MRI and convection-enhanced delivery, may provide new opportunities for treating human brain tumors.

Ultrasound + Targeted Perfluorocarbon Nanoparticles Yield Enhanced Delivery of Drug into Tumor Cells

NCI Alliance for Nanotechnology in Cancer



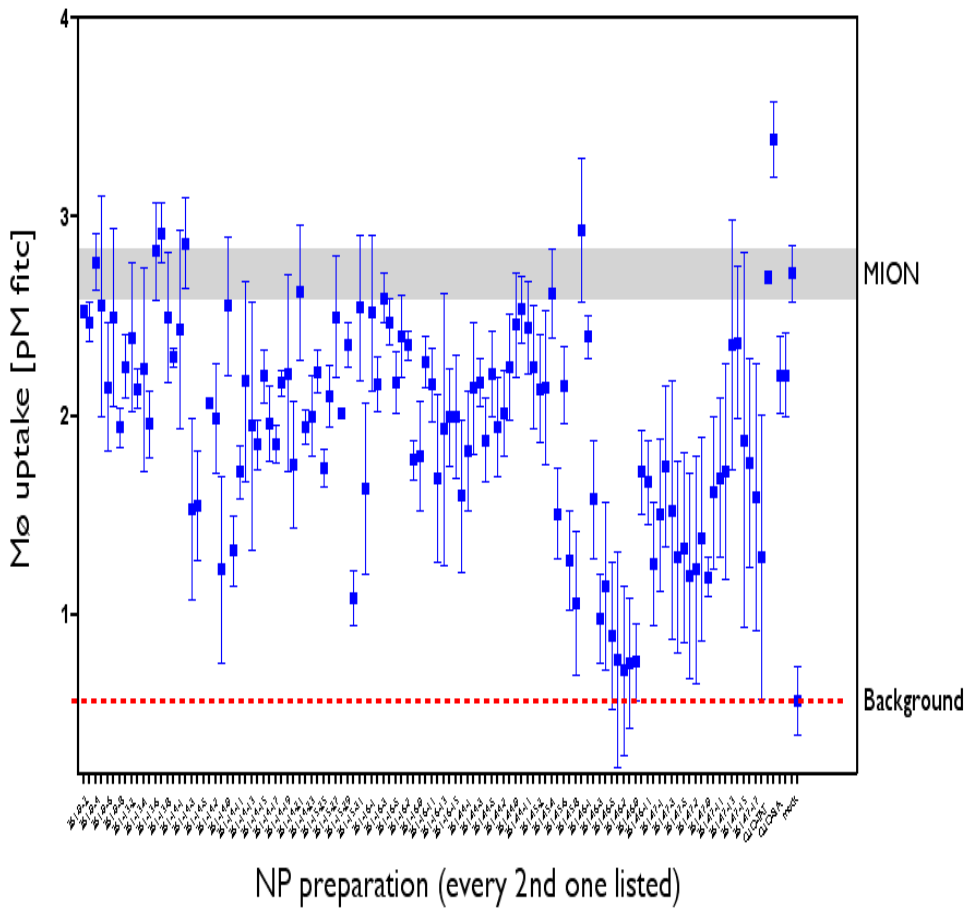
KC Crowder, et al., *Ultrasound in Medicine & Biology*, **31(12) 1693-1700, 2005**

Study Results: Fluorescent dye incorporated in nanoparticles are seen streaming into targeted C32 melanoma cells after five minutes of ultrasound, using commercially available diagnostic ultrasound equipment.

Potential Clinical Advantage: Enhanced, nanoparticle-aided drug delivery using widely available ultrasound equipment could markedly improve the safety of cancer therapy while reducing the amount of drug used and lowering the cost of therapy.

Screening Nanoparticle Libraries for Tumor Targeting Capabilities

NCI Alliance for Nanotechnology in Cancer



Study Results: Nanoparticles decorated with a wide variety of small molecules can be screened to determine which ones escape macrophage uptake and selectively bind to tumors.

Potential Application: New method for creating and screening libraries of decorated nanoparticles permits researchers to identify of tumor-targeting drug delivery vehicles and imaging agents quickly, efficiently, and without prior identification of a tumor-specific marker.

E.Y. Sun, et al., *Bioconjugate Chemistry*, 2006.

Image courtesy of R. Weissleder, Massachusetts General Hospital

Bionanoproducts Under Development

NCI Alliance for Nanotechnology in Cancer

Product	Type of nanomaterial	Indication	Phase	Company
AmBisome	liposome	fungal infections	approved	Gilead Sciences
Doxil	pegylated liposome	metastatic ovarian cancer	approved	OrthoBiotech
VivaGel	dendrimer	topical microbicide for HIV	Phase I	StarPharma
MRX-952	branching block copolymer self-assembled nanoparticulate formulation of irinotecan metabolite	oncology	preclinical	ImaRx Therapeutics
Definity	lipid-encapsulated octofluoropropane nanospheres	echocardiogram contrast agent	approved	ImaRx/BMS
MRX-815	nanobubbles	vascular thrombosis	Phase I	ImaRx
Abraxane	nanoparticulate albumin	non-small cell lung cancer, breast cancer, others	NDA filed	American Pharmaceutical Partners
Cyclosert-camptothecin	cyclodextrin nanoparticle	metastatic solid tumors	IND filed	Insert Therapeutics
TNT-Anti-Ep-CAM	polymer-coated iron oxide	solid tumors	preclinical	Triton BioSystems
Rapamune	nanocrystalline drug	immunosuppressant for kidney transplantation	approved	Elan/Wyeth
Emend	nanocrystalline drug	nausea	approved	Elan/Merck
Leunesse	solid lipid nanoparticles	cosmetics	on market	Nanotherapeutics
Verigene platform	DNA-functionalized gold nanoparticles	diagnostics	on market	Nanosphere
INGN-401	liposome	metastatic lung cancer	Phase I	Introgen
Combidex	iron oxide nanoparticle	tumor imaging	NDA filed	Advanced Magnetics

Source: M. Ferrari, G. Downing, Biodrugs 19, 203 (2005).

There Are Barriers to Rapid Commercialization

NCI Alliance for Nanotechnology in Cancer

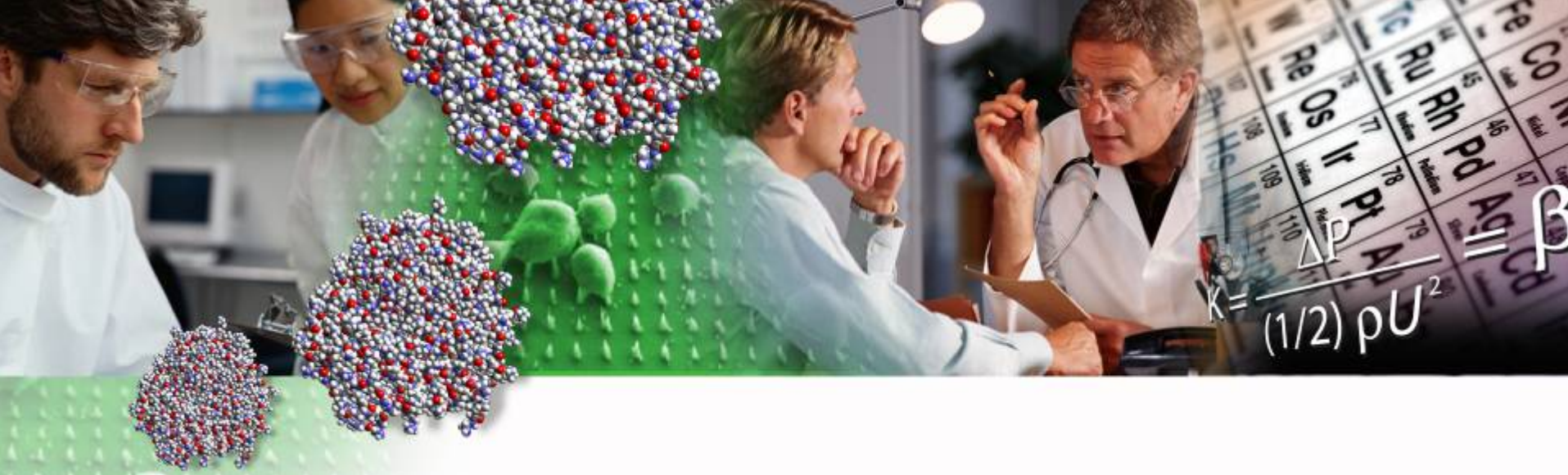
- Culture clash
  - Life sciences and materials sciences typically unconnected
  - Device and biopharmaceutical developers work in different "worlds"
- Business models
  - Classic pharmaceutical, biotech or diagnostic models may need to be modified
- Lack of widespread expertise in nanotechnology
  - Increases risk of large capital investments
- Public Acceptance
  - Disruptive technologies can provoke fear and resistance

Challenge: Regulatory Hurdles

NCI Alliance for Nanotechnology in Cancer

Nano-based products may present new issues for regulatory system:

- Parameters of safety (absorption, distribution, metabolism, elimination) may be different from pharmaceuticals
- Biomedical nanoscale materials are not generally well characterized or standardized at present
- Interactions of nanomaterials with traditional drugs/devices/metabolic pathways are mostly unknown
- Review procedures not accustomed to multifunctional aspects (i.e., Is it a device or a drug? Can the diagnostic and the drug be developed together?)



National Cancer Institute as Catalyst

NCI Launched the Alliance for Nanotechnology in Cancer in 2004

NCI Alliance for Nanotechnology in Cancer

- $144.3M initiative
- Designed to “ignite” nano-product development and commercialization
- Encompasses public and private sectors
- **Six key areas of focus:**
  - **Molecular Imaging and Early Detection**
  - ***In Vivo* Imaging**
  - **Reporters of Efficacy**
  - **Multifunctional Therapeutics**
  - **Prevention and Control**
  - **Research Enablers**

Major Programs of the Alliance

NCI Alliance for Nanotechnology in Cancer

1. **Centers of Cancer Nanotechnology Excellence**
2. **Multidisciplinary Research Teams**
   - Training
   - Interagency Collaborations
3. **Nanotechnology Platforms for Cancer Research**
4. **Nanotechnology Characterization Laboratory**

Nanotechnology Characterization Laboratory (NCL)

NCI Alliance for Nanotechnology in Cancer

- NCL's role:
  - Develop standards and characterization data for nanoscale materials
  - Perform preclinical toxicology, pharmacology, and efficacy testing
  - Facilitate collaborations among the NCI, academia, and the private sector
  - Collaborate with other government agencies to leverage resources and expertise

- http://NCL.cancer.gov

How the Alliance Overcomes Barriers

NCI Alliance for Nanotechnology in Cancer

- Requires academic and commercial partnerships for each supported Alliance project
- Establishes training programs
- Commits major funding that leverages existing infrastructure
- Coordinates with other Federal agencies to leverage NCI funds and creates synergies
- Pre-qualifies new materials and informs standards through the Nanotechnology Characterization Laboratory
- Reduces the risk of investment in new products

Interagency Collaborations: FDA and NCI

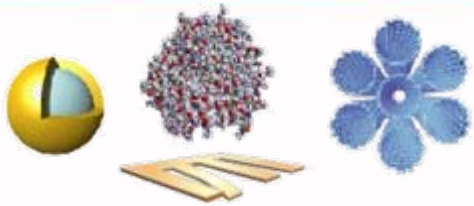
NCI Alliance for Nanotechnology in Cancer

- Hold formal training sessions to keep pace with new research
- Share nanoparticle characterization results
- Optimize the development of new products for cancer
- Collaborate on new draft guidance
- Examine and interpret data on environment, health and safety of nanoparticles

The Alliance: Hallmarks and Operations

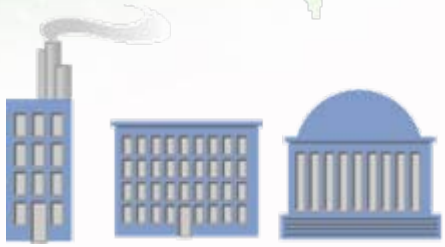
NCI Alliance for Nanotechnology in Cancer

Multidisciplinary Centers of Nanotechnology Excellence



Nanotechnologies

Intra-Agency Collaboration



- University and Medical Centers
- Technology Centers of Excellence
- National Labs
- NCI Technology Development Programs
- Private Sector

Cancer Patients - Clinical Applications

Nanotechnology Characterization Laboratory

- NIST
- FDA
- NCI

Goal Oriented – Project Management

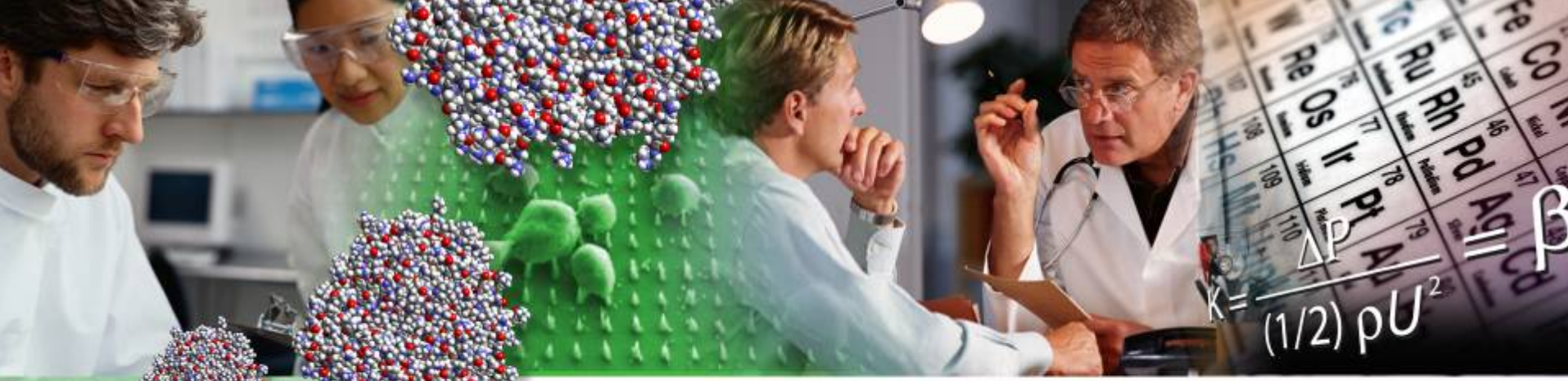
Protocols, Data

Standards

The Alliance Website: nano.cancer.gov

NCI Alliance for Nanotechnology in Cancer

- Timely science advances
- Accessible, comprehensive info
- PubMed Linkages
- Reading room for all audiences
- Dynamic learning environment
- Teaming site for potential collaborations



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